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Clinical Report

Non-Syndromic Hemihyperplasia in a Male and His Mother

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We present two family members with non-syndromal hemihyperplasia (HHP), which developed in adolescence. We have reviewed reported familial cases of HHP and conclude that presentation is similar to sporadi cases and that all affected family members have been related through a maternal relative.

KEY WORDS: hemihypertrophy; familial hemihyperplasia; familial hemihypertrophy

INTRODUCTION

Non-syndromal hemihyperplasia (HHP) is relatively common, but familial inheritance of HHP is rare. We report a family in which the propositus had overgrowth of the left side of his chest compared to the right side and his mother had overgrowth involving her left leg. The enlargement was noted in early adolescence in both family members. The propositus and his mother had increased birthweights (>97th centile) but did not fulfil the diagnostic criteria for Beckwith-Wiedemann syndrome (BWS) or have physical anomalies consistent with a syndromic cause of the HHP. We review previously reported familial cases of non-syndromic HHP and conclude that there are no clinical features allowing differentiation from non-familial cases of HHP.

CLINICAL REPORT

The propositus was the only child born to his parents. Paternal ethnicity was Polish and Irish and maternal ethnicity was Italian. There was no known consanguinity. His mother has since had a miscarriage at 8 weeks of gestation with a second partner.

The pregnancy with the propositus was normal apart from an elevated βHCG level of unknown significance. An ultrasound scan showed a singleton pregnancy. Labor started spontaneously at 42 weeks of gestation and a Cesarean section was performed for failure to progress. Birth weight was 4,700 g (>97th centile). There were no neonatal complications and the propositus had normal developmental milestones.

His chest was described by his mother as normal and symmetric at birth and in early childhood. Asymmetry of the chest was first noted at 11 years of age and had increased over the two years since the asymmetry was first detected (Fig. 1). Radiological studies have shown a normal bony skeleton. The primary dentition erupted normally but his teeth did not fall out spontaneously and required surgical removal. There has been no other significant medical history.

On examination at 13 years of age, he was normally grown. The palpebral fissures were neutral and there were no epicanthic folds. His nose, philtrum, and mouth were normal. There were small gaps between the canine and molar teeth on both sides of the lower jaw but the palate was normally arched and there was no micrognathia. The right side of his chest had underdeveloped musculature in comparison to the left side, and the right nipple was smaller, slightly lower and inverted compared to the left side. Internipple distance was 19 cm (75th centile). There was relative prominence of the left sternum and ribs compared to the right side. The cardiovascular examination was unremarkable. His abdomen had no palpable masses or organomegaly and the genitalia were reported to be normal male. No abnormalities of his hands and feet were present. There was no scoliosis, but a right Sprengel shoulder was noted. Neurological examination was unremarkable. He had an irregular, 2 cm café-au-lait patch under the right axilla and a 1-cm café-au-lait patch on the outer aspect of his right lower leg but there were no other significant dermatological findings. A Panorex of the propositus has shown a crowded upper jaw, but no other obvious dental abnormalities.

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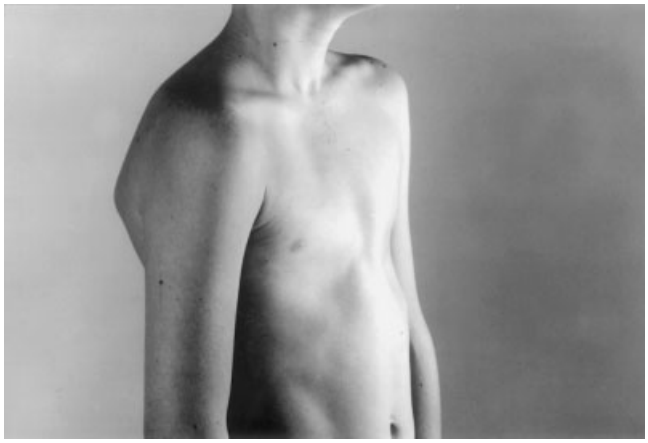

Fig. 1. Chest of the propositus showing asymmetry between the right and left sides with prominence of the left chest and sternum.

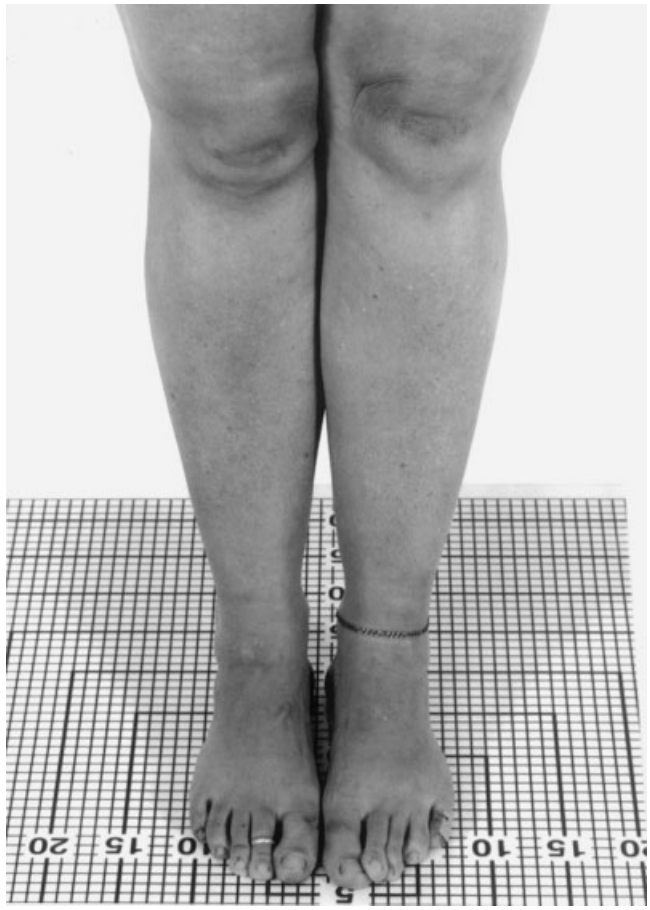

Fig. 2. Legs of the mother of the propositus, showing enlargement of the left leg compared to the right leg.

The pregnancy with the mother of the propositus was complicated by bleeding at 6 weeks of gestation and she was thought to have been one of a twin pregnancy. There were no other significant prenatal events and her birth weight was 4,000 g (90th–97th centile). She was noted to have asymmetry of her leg lengths on a routine physical examination at 11 years of age. Her right leg was described as two inches shorter than her left leg. Surgery was suggested but not pursued by the family and she wore orthotic devices for several years. She has continued to notice the asymmetry regarding wear of her clothing and shoes. Her dental history is unremarkable.

Her past medical history has included hyperthyroidism and thyroid goiter. A thyroid scan showed a solitary nodule and she was treated with medication for one year. A total thyroidectomy was performed at 39 years of age for a multinodular thyroid gland. She had a cholecystectomy at 31 years of age years ago for cholecystitis. Her review of systems was otherwise non-contributory.

On examination, she appeared clinically euthyroid. There were no craniofacial anomalies. There was no evidence of conical teeth or hypodontia and her palate was normally arched. There was no macroglossia. Her cardiovascular examination was unremarkable. Her abdomen had scars from a previous surgical procedure but there were no palpable masses or organomegaly. Her hands and feet were normal. Neurological examination did not show any evidence of weakness or reduced sensation. She had a mild scoliosis convex to the left of the thoracic spine but there were no other bony deformities. There were no significant dermatological findings. Measurements of her axial limb segments showed asymmetry of the lower limbs, with the left leg being 2–5 cm larger than the right leg (Fig. 2; Table I).

The maternal grandmother had primary infertility for 6 years prior to her first pregnancy. She then had two miscarriages at 10 and at 14 weeks of gestation. Her third pregnancy resulted in a healthy male infant. She then miscarried a twin pregnancy at 8 weeks of gestation two months before becoming pregnant with the mother of the propositus. A female maternal cousin of the propositus was described as having a developmental disability. There is no other family history of body asymmetry or dental abnormalities. The maternal grandfather had a brother who fathered twin daughters. Routine chromosome analysis of the mother of the propositus showed an apparently normal female karyotype.

DISCUSSION

Asymmetric overgrowth of one or more body parts or between the left and right sides of the body has been called both HHP and hemihypertrophy in the medical literature [Hoyme et al., 1998; for reviews see Gesell, 1927; Wakefield and Hines, 1933; Gorlin and Meskin, 1962; Cohen, 1989; Ballock et al., 1997; Hoyme et al., 1998; Cohen et al., 2002]. HHP can be non-syndromal (also referred to as isolated HHP) or present as a component of an overgrowth syndrome such as BWS [Elliott and Maher, 1994], Neurofibromatosis type I (NF type I) [Consensus Development Conference, Neurofibromatosis, Conference Statement, 1988], Klippel-Trenaunay syndrome [Cohen, 2000], Proteus syndrome [Biesecker et al., 1999; Cohen et al., 2002], and Silver-Russell syndrome [Price et al., 1999]. The incidence of HHP has been estimated to range between 1:13,200 [Leck et al., 1968] and 1:86,000 [Parker and Skalko,

TABLE I. Physical Measurements of the Propositus and his Mother

	Propositus	Centile	Mother	Centile
OFC	55.8 cm	75th–90th	57.2 cm	>97th
Height	157 cm	50th		
Weight	44 kg	25th–50th		
ICD	3.1 cm	Mean	2.4 cm	−2 SD
IPD	6.3 cm	>97th	5.7 cm	Mean
OCD	10.1 cm	−1 SD	9.9 cm	−1 SD
R upper arm	33.0 cm	75th–90th	37.0 cm	>97th
L upper arm	33.2 cm	75th–90th	36.0 cm	>97th
R forearm	25.0 cm	50th–75th	25.0 cm	75th–90th
L forearm	25.0 cm	50th–75th	25.0 cm	75th–90th
R palm	10.6 cm	75th–97th	11.6 cm	75th–97th
L palm	10.6 cm	75th–97th	11.5 cm	75th–97th
R third finger	8.1 cm	75th–97th	8.1 cm	50th–75th
L third finger	8.1 cm	75th–97th	8.7 cm	50th–75th
R upper leg	45.0 cm	Mean ± 2 SD	48.2 cm	>2 SD
L upper leg	45.0 cm	Mean ± 2 SD	53.0 cm	>2 SD
R lower leg	40.0 cm	50th	43.0 cm	>97th
L lower leg	40.0 cm	50th	45.0 cm	>97th
R foot	23.7 cm	25th	25.2 cm	75th–97th
L foot	23.8 cm	25th	25.7 cm	75th–97th

R, right; L, left; OFC, occiptofrontal circumference; ICD, inner canthal distance; IPD, interpupillary distance; OCD, outer canthal distance.

1969] but syndromic and non-syndromic forms of HHP were not clearly differentiated in these studies [Ballock et al., 1997]. A classification system for HHP based on affected body part(s) has been attempted [Ward and Lerner, 1949; Rowe, 1962; Ringrose et al., 1965] but no subtype of HHP has been clinically correlated with additional phenotypic abnormalities or intellectual development. However, a distinct form of static or mildly progressive HHP with moderate asymmetry and overgrowth can be associated with multiple, subcutaneous lipomas [Biesecker et al., 1998]. Management includes referral to an orthopedic surgeon for consideration of surgical intervention and referral to a geneticist for consideration of syndromal causes of HHP [Ballock et al., 1997].

In this family, the propositus developed asymmetry of his chest and chest musculature in early puberty. There is no other limb asymmetry and apart from delayed dental shedding, no significant medical history. The mother of the propositus was also noted to have leg asymmetry in early adolescence. HHP is usually present at birth, and the development of asymmetry at puberty in both the propositus and his mother is noteworthy. Both affected individuals had high birthweights, previously documented in patients with HHP ascertained because of Wilms tumor [Leisenring et al., 1994]. Despite the high birthweights, the propositus and his mother did not fulfill the diagnostic criteria for BWS [Elliott and Maher, 1994] and the propositus had insufficient café-au-lait spots for the diagnosis of NF type I [Consensus Development Conference, Neurofibromatosis, Conference Statement, 1988]. Underdevelopment of the chest musculature can also be present in Poland anomaly, but the propositus had no significant digital findings and his chest asymmetry was not present at birth. The relationship between the delayed dental shedding and body asymmetry is unknown, although dental abnormalities including enlargement of the teeth and premature eruption of the teeth have been described in patients with HHP with or without facial involvement [Gorlin and Meskin, 1962; Rowe, 1962; Cohen, 1989].

Non-syndromal HHP has been associated with embryonal neoplasia in 3.8% of cases and the spectrum of tumors has included nephroblastoma, adrenocortical carcinoma, and adenoma, hepatoblastoma, neuroblastoma, pheochromocytoma, testicular carcinoma, and undifferentiated sarcoma [Fraumeni et al., 1967; Viljoen et al., 1984; Tomooka et al., 1988; Cohen, 1989; Rattan et al., 1995; Ballock et al., 1997; Cohen et al., 2002]. In one exceptional family, three propositi without asymmetric growth developed Wilms tumor [Meadows et al., 1974]. The mother of the children had asymmetry of the thumbs and lower limb noted from childhood [Meadows et al., 1974]. Bilateral pheochromocytomas were found in a female with congenital HHP who may have had BWS [Van den Akker et al., 2002]. Screening is usually performed until 5 to 10 years of age with abdominal ultrasound and palpation, and therefore, was not indicated for this propositus. Other associations found with non-syndromic HHP are skin lesions [Gorlin and Meskin, 1962], genitourinary anomalies [Viljoen et al., 1984; Cohen, 1989] including medullary sponge kidney [Sprayregen et al., 1973; Saypol and Laudone, 1983; Tomooka et al., 1988], and protein-losing enteropathy with intestinal lymphangiomyoma [Koltuksuz et al., 2000].

Familial recurrence of non-syndromal HHP is rare (Table II) [Reed, 1925; Scott, 1935; Arnold, 1936; Rudolph and Norvold, 1944; Morris and MacGillivray, 1955; Fraumeni et al., 1967; Meadows et al., 1974; Stoll et al., 1993] and in some case reports, affected status of other relatives has been anecdotal. We have summarized the features of reported familial cases in Table II. Although the number of cases remains small to date, it is

TABLE II. Summary of Familial Cases of Isolated Hemihyperplasia (HHP)

Reference	Age at reporting	Birth-weight (g)	FH of twinning	HHP	Intellect	Other	Skin findings	Cyto-genetic studies
Reed, 1925								
Propositus—M	17 y			R side	Normal	Epilepsy		
Sister of propositus	12 y	3,400		R side	IQ = 42	Skin nevi &		
Scott, 1935								
Propositus—F	1 y	2,840		R side		Nevus R shoulder		
Mother of propositus	26.5 y	2,950		L, R side		Scoliosis		
Arnold, 1936								
Propositus—M	5 y			R face	Normal	Early tooth eruption		
Uncle (maternal)*								
Rudolph and Norvold, 1944								
Propositus—F	9.5 y	3,810		L face	Normal	Early tooth eruption		
Mother of propositus								
Grandmother of propositus*								
Morris and MacGillivray, 1955								
(A) Grandmother (maternal)			+	L face				
(A) Propositus				L side	IQ = 42	Scoliosis		
(A) Sister of propositus				L side	IQ = 38	Scoliosis, pes cavus		
(B) Propositus				L side	IQ = 36/ MDP	Scoliosis		
(B) Daughter of propositus				R side	IQ = 41/ MDP	Pes cavus		
Fraumeni et al., 1967								
Propositus—F	7 y 6 m			R side				46, XX
Brother of propositus			+	R leg				
Uncle (maternal)*				R leg				
Meadows et al., 1974								
(1) Propositus						Wilms tumor		
(2) Sib of propositus						Wilms tumor		
(3) Sib of propositus						Renal anomaly		
(4) Sib of propositus						Wilms tumor		
(5) Sib of propositus						<3rd centile		
Mother of propositus				R leg				
Stoll et al., 1993								
Propositus (case 7)—F		3,050		R side	Normal	Scoliosis, SN		46, XX
Mother of propositus								
Our cases								
Propositus—M	13 y	4,700	+	L chest	Normal	Late tooth shedding	Two CAL	
Mother of propositus	37 y	4,000		R leg	Normal			

FH, family history; *anecdotal; CAL, café-au-lait patches; MDP, manic depressive psychosis; SN, supernumerary nipple; &, frequent skin nevi, double row of canine and incisor teeth, high-arched palate.

noteworthy that all affected individuals are related through maternal relatives (Table II). Several families have a history of twinning as described in our pedigree. However, despite the small number of documented familial cases, there are no obvious distinguishing factors in the families that allow clinical separation from sporadic cases of HHP. A high incidence of mental deficiency in early case reports may be related to bias in patient ascertainment.

The range and variability of the clinical abnormalities associated with non-syndromic HHP suggests etiological heterogeneity. Causative theories include chromosomal mosaicism [Gérard-Blanluet et al., 2001] and uniparental disomy [DeBaun et al., 2002] and asymmetry has been reported in diploid/triploid mosaicism [Ferrier et al., 1964] and trisomy 18 mosaicism [Fraumeni et al., 1967]. Vascular malfunction has also been considered as a possible cause and the family history of twinning may be significant. The genes involved in non-syndromic HHP are as yet unknown, although several genes involved in left/right axis determination and thus body asymmetry have been discovered in recent years [reviewed in Cohen, 2001].

CONCLUSION

We have described a family in which the propositus had overgrowth of his left chest and his mother had

overgrowth involving her left leg. The enlargement was not present at birth in either family member. Although both had an increased birthweight, neither satisfied the diagnostic criteria for BWS or an alternative syndromal form of HHP. Although there are few reports of familial HHP, all affected individuals have been related through a maternal relative. We were unable to find physical features differentiating familial and non-familial HHP.

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